Effectiveness of intrauterine insemination in subfertile couples with an isolated cervical factor: a randomized clinical trial

Approximately 10% of couples who wish to have a child fail to conceive within 1 year of regular unprotected intercourse (1). In 5% of these couples, a cervical factor is found during the basic fertility workup (2). The effectiveness of intrauterine insemination (IUI) is well investigated in couples in whom subfertility is caused by a male factor or in whom subfertility is unexplained (3–9). In contrast to the former two indications, data on the effectiveness of IUI for cervical factor subfertility are scarce and conflicting. Four randomized studies have reported on the effectiveness of IUI compared with timed intercourse in couples with cervical-factor subfertility (7, 10–12). Two of these studies clearly indicated a beneficial effect of IUI (10, 12), whereas two others did not report such an effect (7, 11). The discrepancies may be explained by their small sample size, because three of these studies reported on <30 cycles (7, 11, 12). The largest study analyzed 156 cycles, but in 80% of the IUI cycles, as well as in the cycles in which intercourse was advised, ovarian hyperstimulation was given (10). Pooling of the data from these trials could provide a better estimate, but this is not possible because of the quality of the trials and heterogeneity in the participant characteristics and interventions (13). In view of these issues, we assessed the effectiveness of IUI compared with expectant management in couples with isolated cervical-factor subfertility.

Between June 1, 2002 and July 1, 2005, 17 fertility centers in the Netherlands recruited couples with an unfulfilled wish for a child after ≥1 year of frequent unprotected intercourse and in whom the woman had a regular cycle. The study was approved by the local ethics committee of each participating center. A basic fertility workup was performed according to the guidelines of the Dutch Society of Obstetrics and Gynecology and in the same way as reported in our study published elsewhere on the effectiveness of IUI with controlled ovarian hyperstimulation (COH) in unexplained subfertility (14, 15).

After completion of the basic fertility workup, in couples with a cervical factor, diagnosed by means of a well-timed nonprogressive postcoital test (PCT), the prognosis of a spontaneous ongoing pregnancy resulting in a live-born child in the next year was calculated. A nonprogressive PCT was defined as the absence of spermatozoa moving in a straight direction and at functional speed.

The prognosis was calculated according to the prediction model of Hunault et al. (16). This model incorporates the variables of female age, duration of subfertility, primary or secondary subfertility, referral status, and semen analysis results (17). An isolated cervical factor was diagnosed in couples who had a cervical factor and a prognosis of >30%. A prognosis of >30% can only be reached in these couples if no other causes, apart from the abnormal PCT, exist for their declined fertility.

Couples with an isolated cervical factor were eligible for this study. After informed consent, couples were randomly allocated to IUI or to expectant management for 6 months. The randomization sequence was computer generated in balanced-block multiples of two or four, stratified by center. Sequence was concealed, and sealed opaque envelopes were constructed by an independent individual. Clinicians in the participating centers enrolled the couple and subsequently unsealed the first envelope in the sequence. Thereafter, the inclusion was confirmed to the trial coordinator by fax.

Couples allocated to IUI started treatment in the next cycle. Cycle monitoring, detection and/or induction of ovulation, as well as semen preparation and insemination regimens were performed according to hospital-specific...
protocols. The first three IUI cycles were performed without COH, according to the method described in our study on the effectiveness of COH in IUI in couples with an abnormal PCT. If the first three cycles of IUI without COH failed, subsequent IUI cycles were performed with COH. The study protocol recommended the use of FSH for COH. Again, the method was according to that in our other article published in this issue.

Couples allocated to expectant management were followed for 6 months or until an ongoing pregnancy occurred. If no pregnancy occurred, follow-up ended after this period. If a pregnancy miscarried, follow-up continued until the next pregnancy or the end of the 6-month period.

The primary endpoint was ongoing pregnancy within 6 months. Ongoing pregnancy was defined as the presence of fetal cardiac activity at transvaginal sonography, at a gestational age of ≥12 weeks. Secondary endpoints were clinical pregnancies, miscarriages, ectopic pregnancies, multiple pregnancies, and live birth. Clinical pregnancy was defined as the presence of a yolk sac at transvaginal sonography at a gestational age of 7 weeks. Miscarriage was defined as nonvital pregnancy, either seen at transvaginal sonography or as the result of the loss of a visible pregnancy.

We designed our study as a classical superiority trial for ongoing pregnancy rates, because of the anticipated benefits of IUI. The included couples were expected to have a probability of spontaneous ongoing pregnancy in the next 6 months of 15% (i.e., >30% in 12 mo) (18). We assumed that IUI would increase the probability of an ongoing pregnancy in 6 months to 38.5% (19–21). To detect this anticipated difference in ongoing pregnancy rates after 6 months, 50 couples were required in each group (alpha of 5%, power of 80%, 2-sided test).

The analysis was performed according the intention-to-treat principle. Pregnancies occurring in IUI cycles performed within 6 months after randomization were included in the analyses, as well as were spontaneously occurring pregnancies in this period. The treatment effect of IUI was expressed as a relative risk with a 95% confidence interval. We plotted Kaplan-Meier curves to visualize the differences in time to pregnancy between the two groups, and we compared these curves by using a log rank test. In an additional analysis, we evaluated the pregnancy rate per IUI cycle.

In total, 3,894 consecutive couples with a regular cycle underwent a basic fertility workup in one of the participating centers. In 264 couples, an isolated cervical factor was found, and among these, 163 couples were either not invited for participation or declined to participate. Of the other 101 couples, 52 were allocated to IUI, and 49 were allocated to expectant management (Fig. 1). In each group, one woman appeared to have polycystic ovary syndrome, and therefore these women were excluded from the analyses. Baseline characteristics did not differ between the two groups: maternal age was 30 years; duration of subfertility was 1.7 years; 60% of couples had a primary subfertility; FSH was 6.6 IU/L; semen analysis showed a total motile sperm count of 85; and in each group, two women had one-sided tubal occlusion. The mean prognosis in both groups was 37% and 39%, respectively.

No couples were lost to follow-up. Pregnancy data are summarized in Figure 1. In the group allocated to IUI, five (9.8%) women conceived spontaneously before the start of IUI. Four of these pregnancies were ongoing, and one miscarried. Forty-six couples started IUI. Two women (3.9%) conceived spontaneously between IUI cycles. One of these pregnancies was ongoing, and one miscarried. In the first three IUI cycles, 10 (20%) women became pregnant. Nine of these pregnancies were ongoing, and one was an ectopic pregnancy. Thirty couples continued IUI with COH after three cycles of IUI without COH. In the subsequent IUI cycles with COH, eight (16%) women became pregnant. Seven of these pregnancies were ongoing, of which one was a twin pregnancy and one miscarried. Finally, follow-up till live birth was conducted in 19 (86%) of the ongoing pregnancies; all of these pregnancies resulted in live birth of at least one child. In the twin pregnancy, both children were born alive. In two couples, follow-up until live birth was not conducted because the couples changed addresses, and one other woman was still pregnant at the time that the analysis was performed.

In the group allocated to expectant management for 6 months, five (10%) couples started IUI before 6 months: one couple, after 3 months; one couple, after 4.5 months; and three couples, after 5 months of expectant management. One pregnancy occurred in these IUI cycles; this pregnancy was ongoing. Fifteen (31%) women conceived spontaneously during 6 months of expectant management, among whom 12 resulted in an ongoing pregnancy and 3 miscarried. Finally, follow-up till live birth was conducted in 11 (85%) of the ongoing pregnancies; all these pregnancies resulted in the live birth of one child. Two women were still pregnant at the time that the analysis was performed.

After 6 months, 26 pregnancies (51%) had occurred in the group that was allocated to IUI, and 16 pregnancies (33%) had occurred in the group that was allocated to expectant management (Fig. 1). The miscarriage rates in the IUI group and the expectant-management group were 7.7% and 19%, respectively. The number of ongoing pregnancies in the IUI group and the expectant-management group were 22 (43%) and 13 (27%), respectively, resulting in a relative risk of 1.6 (95% confidence interval, 0.91 to 2.8). The number of couples needed to treat with IUI to achieve one additional ongoing pregnancy was 6.2 (95% confidence interval, 3.6 to infinity).

Kaplan-Meier analysis showed a continuous beneficial treatment effect of IUI over expectant management (log rank test P value = .11).
In total, 202 IUI cycles were started in the couples who were allocated to IUI, among which 24 cycles (12%) were canceled. The pregnancy rate per started cycle was 9.4%, with an ongoing-pregnancy rate of 8.4% per started cycle. One hundred thirty-eight IUI cycles without COH were started, among which 11 ongoing pregnancies occurred; this is 8.0% per started cycle. In 64 started IUI cycles with COH, 6 ongoing pregnancies occurred (9.4% per started cycle), of which one was a twin pregnancy.

This randomized clinical trial that evaluated the effectiveness of IUI compared with expectant management suggests that there is a beneficial effect of IUI in couples with an isolated cervical factor.

This study used the prognostic profile of the couple, in addition to diagnosis, as an inclusion criterion. This is important in two ways. First, the inclusion of couples with a prognosis of >30% for an ongoing spontaneous pregnancy ensured that we only included couples with an isolated cervical factor who had no additional causes for their subfertility, apart from the abnormal PCT. Second, the treatment effect in subfertile couples may be dependent not only on diagnosis but also on prognosis (22). By documenting the prognostic profile of the included couples, our study results easily can be extracted and interpreted for each fertility clinic, and the relevance for the individual couple can be judged.

Although this study had a protocol for the performance of PCT and the treatment of IUI, the very fact that 17 centers participated in the trial may have affected the results. Nevertheless, this limitation is relative, because this multicenter approach reflects the performance of the PCT and the effectiveness of IUI in daily fertility practice.

The PCT has been abandoned in many guidelines (23, 24). This is based on the results of one randomized clinical trial, in which the effectiveness of the PCT was assessed by comparing a strategy in which all couples had a PCT with a strategy in which none of the couples had a PCT (25). Those investigators concluded that the performance of the PCT resulted in more interventions, without an increase in pregnancy rates. This clinical trial has been criticized by several investigators for the following reasons: the included sample was not sufficiently exclusive (20% of women had an ovulatory disorder), the PCT was not performed in all couples who were allocated to the strategy in which all couples had a PCT with a strategy in which none of the couples had a PCT (25).

FIGURE 1

Flowchart of trial population, with inclusion and outcome. Ong = ongoing; EP = ectopic pregnancy; IUI = intrauterine insemination.
case of an abnormal PCT. However, IUI without COH was not provided in this study, whereas IUI with COH and even IVF were given instead. These methodological problems may have influenced the outcome and interpretation of that trial (29). Last, the occurrence of multiple pregnancies was not studied. This is worrisome, because treatment with IUI was always performed with ovarian hyperstimulation.

Abandoning the PCT as a component in the basic fertility workup means that couples with an isolated cervical factor can no longer be identified. A misdiagnosis would lead to expectant management, resulting in lower pregnancy rates, as demonstrated by our trial, or to IUI with controlled ovarian hyperstimulation, which increases the risk of multiple pregnancies. From our study, we can calculate that 20 PCTs are needed to identify one couple with an isolated cervical factor. A model for predicting the PCT result has been published elsewhere (7, 30). By using this model, it is necessary to perform even fewer PCTs to identify those couples with an isolated cervical factor.

Pieter Steures, M.D. a,b,c Jan Willem van der Steeg, M.D. a,b,c Peter G. A. Hompes, M.D., Ph.D. a Patrick M. M. Bossuyt, Ph.D. d J. Dik F. Hab huma, Ph.D. e Marinus J. C. Eijkemans, Ph.D. c Willem A. Schöls, M.D. e Jan M. Burggraff, M.D. f Fulco van der Veen, M.D., Ph.D. b Jan W. J. Mol, M.D., Ph.D. b,g For CECERM (Collaborative Effort for Clinical Evaluation in Reproductive Medicine)

a Department of Obstetrics and Gynecology, Vrije Universiteit Medical Center, Amsterdam; b Center for Reproductive Medicine Academic Medical Center, Amsterdam; c Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam; d Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam; e Department of Obstetrics and Gynecology, Meander Medical Center, Amersfoort; f Department of Obstetrics and Gynecology, Schepersharenhuis, Emmen; and g Department of Obstetrics and Gynecology, Máxima Medical Center, Veldhoven, the Netherlands

REFERENCES


APPENDIX

The CECERM (Collaborative Effort for Clinical Evaluation in Reproductive Medicine) study group investigators and their participating centers in the Netherlands are as follows:

P. F. M. van der Heijden (Twenteborg Ziekenhuis, Almelo)

W. A. Schöls (Meander Medisch Centrum, Amersfoort)

M. H. Mochtar (Academisch Medisch Centrum, Amsterdam)

H. R. Verhoeve (Onze Lieve Vrouwe Gasthuis, Amsterdam)

P. G. A. Hompes (Vrij Universiteit Medisch Centrum, Amsterdam)

L. J. van Dam (Gelre Ziekenhuis, Apeldoorn)

A. V. Sluijmer (Wilhelmina Ziekenhuis, Assen)

R. E. Bernardus (Ziekenhuis Gooi-Noord, Blaricum)

M. C. S. Vermeer (Amphia Ziekenhuis Breda, Breda)

J. M. Burggraaff (Scheper Ziekenhuis, Emmen)

G. J. E. Oosterhuis (Medisch Spectrum Twente, Enschede)

F. M. C. Delemarre (Elkerliek Ziekenhuis, Helmond)

H. J. H. M. Van Dessel (TweeSteden Ziekenhuis, Tilburg/Waalwijk)

F. J. M. Broekmans (UMC Utrecht, Utrecht)

C. A. M. Koks (Máxima Medisch Centrum, Veldhoven)

P. Bourdrez (Vie Curi Medisch Centrum, Venlo/Venray)

W. W. J. Riedijk (Zaans Medisch Centrum, Zandam)